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Alcohol consumption and risk of lung cancer: a pooled analysis of cohort studies[1–3]

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ABSTRACT

Background: Although smoking is the primary cause of lung cancer, much is unknown about lung cancer etiology, including risk determinants for nonsmokers and modifying factors for smokers.

Objective: We hypothesized that alcohol consumption contributes to lung cancer risk.

Design: We conducted a pooled analysis using standardized exposure and covariate data from 7 prospective studies with 399 767 participants and 3137 lung cancer cases. Study-specific relative risks (RRs) and CIs were estimated and then combined to calculate pooled multivariate RRs by using a random-effects model.

Results: We found a slightly greater risk for the consumption of ≥30 g alcohol/d than for that of 0 g alcohol/d in men (RR: 1.21; 95% CI: 0.91, 1.61; *P* for trend = 0.03) and in women (RR: 1.16; 95% CI: 0.94, 1.43; *P* for trend = 0.03). In male never smokers, the RR for consumption of ≥15 g alcohol/d rather than 0 g alcohol/d was 6.38 (95% CI: 2.74, 14.9; *P* for trend < 0.001). In women, there were few never-smoking cases and no evidence of greater risk (RR: 1.35; 95% CI: 0.64, 2.87). Because of possible residual confounding by smoking, we performed sensitivity analyses by reclassifying the never smokers in the highest drinking category as former smokers. Resulting associations for alcohol consumption were somewhat attenuated, but *P* for trend = 0.05 for men, which was near the original *P* = 0.03.

Conclusions: A slightly greater risk of lung cancer was associated with the consumption of ≥30 g alcohol/d than with no alcohol consumption. Alcohol consumption was strongly associated with greater risk in male never smokers. Residual confounding by smoking may explain part of the observed relation. *Am J Clin Nutr* 2005;82:657–67.

KEY WORDS Alcohol consumption, diet, epidemiology, lung neoplasms, meta-analysis

INTRODUCTION

There is clear evidence that smoking causes lung cancer, but much about the etiology of lung cancer is not well understood, including why some nonsmokers develop lung cancer and why only a portion of smokers do so. It has been suggested that some of this variation may be explained by alcohol consumption (1, 2). Alcohol is oxidized to acetaldehyde, a known carcinogen (3). There is evidence that alcohol can act as a prooxidant in tissues, including lung tissue (4–12), and on lipids, including lung membrane lipids (4, 13). Alcohol can induce the expression of enzymes that are related to carcinogen metabolism (14), and compounds other than ethanol that are contained in alcoholic beverages may have carcinogenic effects.

In studies of alcoholics, morbidity and mortality due to lung cancer have been shown to be high (15–21), but the greater risk may be explained, in part or entirely, by the fact that the people in these populations were also more likely to smoke. Most studies of alcoholics have not controlled for the smoking status of participants. In studies measuring both alcohol consumption and smoking in individuals, there is some (although inconsistent) evidence of a modest increase in lung cancer risk in association with alcohol consumption (2, 22). In a meta-analysis, there was evidence of a greater risk of lung cancer associated with heavier drinking in cohort and hospital-based case-control studies but not in population-based case-control studies (22). Many studies examining alcohol and lung cancer have been limited by small

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TABLE 1
Characteristics of the cohort studies included in the pooled analysis of alcohol and lung cancer

Study	Follow-up period	Baseline cohort size[1]	Age range	Lung cancer cases	Alcohol intake in drinkers[2]	Drinkers
		n	*y*	*n*	*g/d*	%
Alpha-Tocopherol Beta-Carotene Cancer Prevention Study, men	1985–1996	6771[3]	50–69	298	20.2 ± 21.8	89
Canadian National Breast Screening Study, women	1980–1993	56 837	40–59	149	10.9 ± 14.5	77
Health Professionals Follow-Up Study, men	1986–1996	44 349	40–75	244	14.8 ± 16.1	76
Iowa Women's Health Study, women	1986–1996	33 831	55–69	433	8.7 ± 12.3	45
Netherlands Cohort Study						
Women	1986–1992	62 412	55–69	128	8.5 ± 10.6	68
Men	1986–1992	58 279	55–69	828	17.1 ± 16.6	85
New York State Cohort						
Women	1980–1987	21 045	15–107	130	6.0 ± 9.4	78
Men	1980–1987	27 936	15–107	392	12.1 ± 17.0	89
Nurses' Health Study, women						
Section A	1980–1986	88 307	34–59	156	9.4 ± 11.6	68
Section B	1986–1996	68 307[4]	40–65	379	9.6 ± 12.0	64
Total		399 767		3137		

[1] After exclusion of participants with incomplete alcohol intake data, implausible values for energy intake, or previous diagnosis of cancer (other than nonmelanoma skin cancer). Participants were also excluded if data regarding smoking status, smoking duration (for current and past smokers), or smoking dose (for current smokers) were missing.

[2] $\bar{x}$ ± SD. In the United States, there is 12.8 g alcohol in 12 oz (335 mL) beer, 10.9 g alcohol in 4 oz (118 mL) wine, and 14.0 g alcohol in 1.5 oz (44 mL) 80-proof spirits.

[3] Only the placebo group of the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study was included.

[4] The participants in the baseline cohort for the Nurses' Health Study Section B are included in the Nurses' Health Study Section A and are not included in the total.

sample size, particularly with respect to heavy drinkers. Furthermore, given the correlation between alcohol consumption and smoking, the examination of the effect of alcohol in never smokers is particularly informative. However, most studies have not been able to examine risk in this group because of the small numbers of lung cancer cases identified in never smokers. In the Pooling Project of Prospective Studies of Diet and Cancer (23-25), the primary data from 7 cohort studies of diet and cancer have been reanalyzed by using standardized categories of alcohol consumption and of all potential covariates including the smoking variables. These data allow for the examination of subgroups of interest to address the issue of a possible association of alcohol consumption with lung cancer. We report here pooled results from these cohorts with respect to the association between alcohol consumption and the risk of lung cancer.

SUBJECTS AND METHODS

Methods for the Pooling Project of Prospective Studies of Diet and Cancer have been described previously (23–25). The Pooling Project was originally designed to examine associations between dietary factors and breast cancer risk. It has now been expanded to include analyses related to other cancer sites, and it therefore includes cohorts of men. Inclusion criteria for cohort studies in the pooled analyses of lung cancer were ≥50 incident cases of lung cancer, an assessment of usual diet, a validation study of the diet instrument or of a closely related instrument, and assessment of smoking status at baseline. For these analyses related to lung cancer, 2 cohorts included previously in the breast cancer analyses [the New York University Women's Health Study (26) and the Swedish Mammography Cohort (27)] were not included because smoking data were not collected at baseline. In addition, as in the previous study of alcohol and breast cancer (24), the Adventist Health Study (28) was not included because of the low prevalence of alcohol consumption in that population. Each of the studies included here had been reviewed and approved by the institutional review board of the institution at which the study was conducted.

As shown in **Table 1**, included in this report were 5 cohorts with women [the Canadian National Breast Screening Study (29), the Iowa Women's Health Study (1), the Netherlands Cohort Study (30), the New York State Cohort (31), and the Nurses' Health Study (NHS; 32, 33)] and 4 cohorts with men [the α-Tocopherol β-Carotene Cancer Prevention Study (ATBC; 34), the Health Professionals Follow-up Study (32, 33), the Netherlands Cohort Study (30), and the New York State Cohort (31)]. Because there were repeated assessments of smoking and alcohol consumption for the NHS, this cohort has been analyzed in 2 sections: NHS Section A, including the 1980–1986 follow-up, and NHS Section B, including the 1986–1996 follow-up. Incident cases from the NHS were counted in just one of the cohorts (although a woman could contribute person-time as a noncase to NHS Section A and become a case in NHS Section B). Because the person-time in the different time periods was asymptotically uncorrelated even though the data were based on the same participants (35), the use of pooled estimates from the 2 time periods did not differ from the use of estimates from a single time period but had the advantage of using the updated exposure data from 1986.

Lung cancer outcome ascertainment

Each study ascertained incident lung cancers by using follow-up questionnaires with subsequent medical record review

(32), linkage with a cancer registry (1, 29–31) or both (34). In addition, some studies used mortality registries or death certificates (1, 29, 31, 32, 34). We categorized lung cancer on the basis of the International Classification of Diseases for Oncology morphology codes (36) or the histologic classification provided by the original study investigators.

Alcohol consumption assessment

For most of the cohorts, alcohol consumption was assessed with queries regarding the consumption of beer, wine, and spirits. Some of the questionnaires included information regarding red and white wine or other specific beverages. For the New York State Cohort, only total alcohol consumption was queried; this cohort was not included in beverage-specific analyses. The format of the questionnaires varied. Some allowed participants to indicate both frequency of drinking and the usual number of drinks on each occasion; others asked participants to choose among categories indicating total usual alcohol consumption. Most of the questionnaires assumed a standard drink size; the Canadian National Breast Screening Study allowed participants to indicate a drink size that differed from the standard indicated, and the ATBC Study allowed participants to choose from 1 of 3 portion-size options. Alcohol consumption in grams per day was calculated for each study by using the reported frequency of consumption, the beverage-specific alcohol content, and the average amount consumed.

Smoking assessment

For each cohort, baseline cigarette smoking status (never, current, or former smoker) was assessed. The ATBC Study (34) was limited by design to men who were currently smokers. For all of the cohorts, data were also obtained regarding duration of smoking in those who had ever smoked. For most studies, the information about the amount smoked was the amount of smoking at baseline. For the New York State Cohort, the usual number of cigarettes smoked daily was ascertained. Because few of the studies included questions regarding pipes, cigars, and other tobacco products, only cigarette smoking was considered here. Only the Netherlands Cohort Study included a detailed assessment of passive smoking.

Statistical analysis

For each dataset, after applying the exclusion criteria used by that study, we further excluded participants if they reported a history of cancer (other than nonmelanoma skin cancer) at baseline, were missing information regarding alcohol consumption, reported energy intakes either $>$ or $<$ 3 SDs from the study-specific $\log_e$-transformed mean energy intake of the baseline population, or were lacking information on smoking status, the number of years of smoking by past and current smokers, or the number of cigarettes smoked daily by current smokers.

We examined risk related to alcohol consumption by using the Cox proportional hazards model (37). Relative risks (RRs) were estimated for categories of total alcohol consumption and for consumption of alcohol from beer, wine, and spirits. *P* for trend across categories was calculated by taking the study-specific median for each category and assigning that value to all the participants in that category. This variable was then entered into the regression model.

Incidence rate ratios for the ATBC Study, the Health Professionals Follow-up Study, the Iowa Women's Health Study, the New York State Cohort, and the NHS were estimated by using SAS PROC PHREG software (version 8.2; SAS Institute, Cary, NC; 38). For the Canadian National Breast Screening Study and the Netherlands Cohort Study, the analysis was of a case-cohort study (39) and used EPICURE software (version 2.11; Hirosoft, Seattle, WA; 40). In all the studies, age at baseline and the year that the baseline questionnaire was returned were included as stratification variables. Person-years of follow-up were calculated from the date the baseline questionnaire was returned until the date of lung cancer diagnosis, the date of death, or the end of follow-up, whichever came first.

We compared the following approaches for controlling for confounding by smoking: adjustment for smoking status, adjustment for pack-years smoked, adjustment for smoking status and duration of smoking, and adjustment for smoking status, duration of smoking, and amount smoked. Of these, the last model (ie, smoking status, duration of smoking, and amount smoked) explained more of the variation in risk than did the others, and it is the one reported here.

Because of differences between men and women in the distribution of alcohol consumption and of beverage-specific use, we conducted sex-specific analyses. For the cohorts that included both men and women, ie, the Netherlands Cohort Study and New York State Cohort, men and women from each cohort were analyzed separately. All RRs were adjusted for smoking status (never, past, or current), smoking duration (for past and current smokers; continuous), amount smoked (for current smokers; continuous), education ($<$high school graduate, high school graduate, or $>$high school graduate), body mass index (in kg/m^2) ($<$23, 23 to $<$25, 25 to $<$30, or $\geq$30), and energy intake (continuous). We had previously found fruit intake and β-cryptoxanthin to be inversely associated with the risk of lung cancer (25, 41). We examined confounding by both of these factors but found that results were very similar with and without inclusion of either the fruit or β-cryptoxanthin variable; results reported here are without adjustment for either of these dietary variables. An indicator variable for missing responses for covariates was created, when applicable. There was missing information for $\leq$7% of participants for each variable within each study. Two-sided 95% CIs and *P* values were calculated. We used the random-effects model to combine the $\log_e$ RRs; study-specific RRs were weighted by the inverse of their variance (42).

Heterogeneity among studies was calculated by using the *Q* statistic (42, 43). For analysis of associations between specific types of alcoholic beverages and lung cancer, a test for between-study heterogeneity was carried out simultaneously on all alcoholic beverages (beer, wine, and spirits); the results were not statistically significant. A contrast test based on the beverage-specific associations and their estimated covariance matrix was used to test for differences between the associations. This test statistic approximately follows a chi-square distribution with 2 df.

For total alcohol consumption, risk was calculated according to strata of smoking status and several dietary variables. We examined analyses stratified by intake of fruit and of β-cryptoxanthin because of the previous finding that each was inversely associated with risk of lung cancer in the Pooling Project (25, 41). We examined risks within strata of folate intake because of interactions between folate and alcohol at the level of absorption and metabolism (44) and examined risks within strata

TABLE 2
Smoking habits by alcohol consumption category and by study[1]

	Men				Women					
	ATBC	HPFS	NLCS	NYSC	CNBSS	IWHS	NLCS	NYSC	NHS-A	NHS-B
Alcohol consumption										
0 g/d										
Never smokers (%)	0	62	22	44	63	75	73	71	57	57
Current smokers (%)	100	7	33	16	17	11	15	13	22	17
Cigarettes smoked/d (n)[2]	20 ± 9[3]	22 ± 12	16 ± 9	25 ± 13	19 ± 11	19 ± 10	12 ± 8	20 ± 11	21 ± 10	20 ± 11
>0 to <5 g/d										
Never smokers (%)	0	54	20	34	57	66	68	52	45	45
Current smokers (%)	100	7	27	18	18	13	16	21	27	19
Cigarettes smoked/d (n)[2]	18 ± 8	20 ± 12	16 ± 7	23 ± 12	18 ± 8	18 ± 9	12 ± 7	19 ± 11	19 ± 10	19 ± 10
5 to <15 g/d										
Never smokers (%)	0	45	16	27	47	48	44	35	33	33
Current smokers (%)	100	9	28	20	20	23	26	31	33	24
Cigarettes smoked/d (n)[2]	19 ± 8	20 ± 12	15 ± 8	23 ± 12	18 ± 9	18 ± 10	12 ± 8	19 ± 12	19 ± 11	19 ± 11
15 to <30 g/d										
Never smokers (%)	0	38	7	22	35	38	33	22	27	27
Current smokers (%)	100	9	39	25	27	26	32	42	35	26
Cigarettes smoked/d (n)[2]	21 ± 8	19 ± 12	16 ± 9	24 ± 12	18 ± 10	19 ± 10	15 ± 10	19 ± 11	20 ± 11	19 ± 10
≥30 g/d										
Never smokers (%)	0	25	6	15	29	22	15	16	18	19
Current smokers (%)	100	20	43	36	33	51	55	52	54	43
Cigarettes smoked/d (n)[2]	24 ± 10	23 ± 13	19 ± 11	28 ± 13	19 ± 10	23 ± 11	15 ± 9	23 ± 12	24 ± 12	23 ± 11

[1] ATBC, Alpha-Tocopherol Beta-Carotene Cancer Prevention Study; HPFS, Health Professionals Follow-Up Study; NLCS, Netherlands Cohort Study; NYSC, New York State Cohort; CNBSS, Canadian National Breast Screening Study; IWHS, Iowa Women's Health Study; NHS-A and NHS-B, Nurses' Health Study Section A and Section B, respectively.
[2] By current smokers.
[3] $\bar{x}$ ± SD (all such values).

of vitamin A intake because of previous findings of differences in risk associated with alcohol depending on vitamin A status (45). We tested whether there were differences in the RRs between the strata by using a meta-regression model (46). We also tested whether associations differed between adenocarcinomas, small cell carcinomas, and squamous cell carcinomas by using a 2-df Wald test statistic (47). Collectively, these 3 histologic types represented ≥60% of the cases in each study.

RESULTS

This study included 7 cohorts with 399 767 participants and 3137 lung cancer cases (1375 females and 1762 males) (Table 1). Drinking rates varied among the cohorts. Mean drinking was highest in the ATBC Study and lowest in the cohorts of women. The Iowa Women's Health Study had the largest percentage who reported being nondrinkers (55%). Nearly half of the male cases were members of the Netherlands Cohort Study. Among the female cases, the largest number came from the Iowa Women's Health Study and the NHS.

As shown in **Table 2**, there was a tendency for the prevalence of smoking to increase with greater alcohol consumption; the proportion of never smokers decreased and that of current smokers increased. However, the amount smoked by smokers was similar in each category although somewhat higher for the highest category of alcohol. The one exception was the ATBC Study, which was limited to smokers, such that, at every level of alcohol consumption, 100% of the subjects were smokers. The correlation between alcohol consumption in drinkers and cigarettes smoked daily in current smokers ranged from 0.09 in the females in the New York State Cohort to 0.24 in the subjects (all of whom were male) of the ATBC Study; the median correlation in the cohorts was 0.16, and all correlations were significant (data not shown).

Study-specific and pooled multivariate RRs of lung cancer in relation to alcohol consumption are shown in **Table 3**. In models adjusted only for age, the pooled RRs for consumption of ≥30 g alcohol/d compared with no alcohol consumption were 1.76 (95% CI: 1.15, 2.67) in men and 3.09 (95% CI: 2.06, 4.63) in women. In multivariate models that included adjustment for smoking, the pooled RRs associated with reported consumption of ≥30 g alcohol/d compared with no alcohol consumption were 1.21 (95% CI: 0.91, 1.61) in men and 1.16 (95% CI: 0.94, 1.43) in women; neither of these values was statistically significant. For both men and women, the test for trend in this association was statistically significant ($P = 0.03$). The heterogeneity by sex was not statistically significant ($P = 0.72$ for between-studies heterogeneity due to sex for ≥30 g alcohol/d category); the pooled estimate for men and women combined was 1.18 (95% CI: 1.00, 1.39) in a comparison of consumption of ≥30 and 0 g alcohol/d (data not shown). Among the men, when the analysis excluded those cases diagnosed within 4 y of the baseline data collection, the pooled multivariate RR for the upper category of consumption was 1.48 (95% CI: 0.96, 2.29; P for trend = 0.02). There was significant heterogeneity among the cohorts for this analysis ($P = 0.04$). In the corresponding analysis in women, the RR was slightly closer to the null than it was when all cases were included; the results were not statistically significant (pooled multivariate RR: 1.06; 95% CI: 0.83, 1.35; P for trend = 0.16).

TABLE 3
Alcohol consumption (g/d) and lung cancer: study-specific and pooled multivariate-adjusted relative risks (RR)[1]

	Alcohol consumption (g/d)					*P* for trend	*P* for between-studies heterogeneity for ≥30 g alcohol/d category
	None	>0 to <5	5 to <15	15 to <30	≥30		
Men							
Alpha-Tocopherol Beta-Carotene Cancer Prevention Study							
No. of cases	45	61	79	60	53	0.59	
RR	1.0	0.82	0.87	0.81	0.83		
95% CI	—	0.56, 1.22	0.60, 1.27	0.54, 1.20	0.55, 1.26		
Health Professionals Follow-Up Study							
No. of cases	51	41	67	18	67	0.10	
RR	1.0	0.80	0.97	0.51	1.26		
95% CI	—	0.53, 1.21	0.67, 1.40	0.29, 0.87	0.86, 1.84		
Netherlands Cohort Study							
No. of cases	111	136	200	193	188	0.01	
RR	1.0	1.11	1.20	1.10	1.69		
95% CI	—	0.78, 1.57	0.86, 1.66	0.79, 1.54	1.18, 2.44		
New York State Cohort							
No. of cases	47	135	86	53	71	0.01	
RR	1.0	0.73	0.95	0.85	1.16		
95% CI	—	0.52, 1.02	0.66, 1.36	0.57, 1.26	0.80, 1.70		
Pooled							
No. of cases	254	373	432	324	379	0.03	0.09
RR	1.0	0.86	1.00	0.83	1.21		
95% CI	—	0.71, 1.03	0.84, 1.20	0.62, 1.10	0.91, 1.61		
Pooled[2]							
No. of cases	110	184	228	158	197	0.02	0.04
RR	1.0	0.99	1.18	1.01	1.48		
95% CI	—	0.76, 1.28	0.86, 1.62	0.77, 1.31	0.96, 2.29		
Women							
Canadian National Breast Screening Study							
No. of cases	32	42	28	19	28		
RR	1.0	0.96	0.71	0.83	1.12	0.65	
95% CI	—	0.57, 1.62	0.39, 1.26	0.43, 1.59	0.59, 2.13		
Iowa Women's Health Study							
No. of cases	197	79	57	31	69		
RR	1.0	0.74	0.78	1.03	1.49	<0.01	
95% CI	—	0.57, 0.96	0.58, 1.05	0.70, 1.51	1.11, 2.00		
Netherlands Cohort Study							
No. of cases	43	30	24	22	9		
RR	1.0	0.59	0.57	0.77	0.56	0.55	
95% CI	—	0.34, 1.01	0.31, 1.07	0.38, 1.54	0.21, 1.45		
New York State Cohort							
No. of cases	25	66	19	12	8		
RR	1.0	0.91	0.89	0.85	1.04	0.99	
95% CI	—	0.57, 1.45	0.48, 1.64	0.42, 1.74	0.46, 2.38		
Nurses' Health Study							
Section A							
No. of cases	50	40	32	11	23		
RR	1.0	0.77	0.64	0.63	0.99	>0.99	
95% CI	—	0.50, 1.17	0.41, 1.00	0.32, 1.21	0.59, 1.65		
Section B							
No. of cases	120	87	92	35	45		
RR	1.0	0.81	1.04	1.03	1.07	0.32	
95% CI	—	0.61, 1.06	0.79, 1.37	0.70, 1.51	0.75, 1.52		
Pooled							
No. of cases	467	344	252	130	182		
RR	1.0	0.78	0.81	0.92	1.16	0.03	0.35
95% CI	—	0.67, 0.91	0.68, 0.97	0.74, 1.13	0.94, 1.43		
Pooled[2]							
No. of cases	297	211	163	90	108		
RR	1.0	0.78	0.84	1.00	1.06	0.16	0.56
95% CI	—	0.65, 0.94	0.69, 1.03	0.77, 1.29	0.83, 1.35		

[1] Adjusted for education (<high school graduate, high school graduate, or >high school graduate), BMI (<23, 23 to <25, 25 to <30, or ≥30; in kg/m^2), energy intake (continuous), smoking status (never, past, or current), smoking duration for past and current smokers (continuous), and cigarettes smoked daily for current smokers (continuous).

[2] Excluding first 4 y of follow-up.

TABLE 4
Risk of lung cancer associated with alcohol consumption from beer, wine, and spirits by sex: pooled multivariate-adjusted relative risks (RR)[1]

	Alcohol consumption (g/d)				*P* for trend	*P* for between-studies heterogeneity in ≥15 g alcohol/d category	*P* for between-studies heterogeneity due to beverage type in ≥15 g alcohol/d category
	None	>0 to <5	5 to <15	≥15			
Men							
Beer							
No. of cases	613	412	227	118			
RR	1.0	0.90	0.82	1.10	0.47	0.47	
95% CI	—	0.77, 1.05	0.67, 0.99	0.85, 1.42			
Wine							
No. of cases	861	348	103	58			
RR	1.0	0.94	0.66	0.87[2]	0.04	0.23	
95% CI	—	0.80, 1.11	0.51, 0.87	0.55, 1.39			
Spirits							
No. of cases	435	304	271	360			
RR	1.0	1.17	1.00	1.34	0.04	0.28	0.03
95% CI	—	0.98, 1.40	0.83, 1.21	1.09, 1.66			
Women							
Beer							
No. of cases	947	122	102	74			
RR	1.0	0.75	1.18	1.88	<0.001	0.43	
95% CI	—	0.62, 0.92	0.95, 1.46	1.45, 2.42			
Wine							
No. of cases	699	379	100	67			
RR	1.0	0.87	0.75	1.09	0.99	0.31	
95% CI	—	0.72, 1.05	0.52, 1.07	0.78, 1.51			
Spirits							
No. of cases	768	224	138	115			
RR	1.0	0.86	0.77	0.99	0.52	0.56	<0.01
95% CI	—	0.73, 1.00	0.56, 1.06	0.80, 1.22			

[1] Adjusted for education (<high school graduate, high school graduate, or >high school graduate), BMI (<23, 23 to <25, 25 to <30, or ≥30; in kg/m^2), energy intake (continuous), smoking status (never, past, or current), smoking duration for past and current smokers (continuous), and cigarettes smoked daily for current smokers (continuous). Each analysis is also adjusted for consumption of the other 2 beverages (eg, beer is also adjusted for wine and spirits).

[2] The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study had no cases in the ≥15 g alcohol/d category and was not included in this category but was included in the 2 lower categories.

Risks associated with specific beverages are shown in **Table 4**. For these analyses, because of the small numbers of heavy drinkers of a single beverage, the upper category was collapsed to those drinking ≥15 g alcohol of that beverage daily. There was significant between-studies heterogeneity for sex in the ≥15 g/d category for alcohol from beer ($P = 0.004$) and spirits ($P = 0.03$) but not from wine ($P = 0.24$) (data not shown). In men, there was no increase in risk associated with alcohol from beer. For alcohol from wine, there was evidence of decreased risk (pooled multivariate RR: 0.87; 95% CI: 0.55, 1.39; *P* for trend = 0.04). When men drinking ≥15 g alcohol/d from spirits were compared with those who drank no spirits, the pooled multivariate RR was1.34 (95% CI: 1.09, 1.66; *P* for trend = 0.04). Because there were many cases in the consumption category of ≥15 g alcohol/d, we also examined the risk of lung cancer in men who consumed 15 to <30 (pooled multivariate RR: 1.15; 95% CI: 0.87, 1.51) and ≥30 (pooled multivariate RR: 1.65; 95% CI: 1.19, 2.27) g alcohol/d from spirits (*P* for trend = 0.012; data not shown). There was significant heterogeneity among men in the associations of the 3 beverage types with risk of lung cancer ($P = 0.03$ for consumption of ≥15 g alcohol/d). In women, among those drinking ≥15 g alcohol from beer/d, the pooled multivariate RR was 1.88 (95% CI: 1.45, 2.42; *P* for trend < 0.001). The CIs included the null for the other 2 beverages for the upper category RR estimates. For women, the *P* value for heterogeneity among the 3 beverages in the upper category of consumption was < 0.01. Separate data on the consumption of red and white wine were available for a subset of studies; these separate results were similar to those shown for total wine consumption by both men and women (data not shown).

RRs for lung cancer stratified by smoking status are shown in **Table 5**. The ATBC Study had no participants who were never or former smokers, and thus it was not included in analyses for those categories. The Canadian National Breast Screening Study and the New York State Cohort were not included in the highest drinking category for never smokers because of insufficient sample size, but they were included in the other categories. Also in these analyses, because of limitations of sample size, the highest category of consumption was ≥15 g alcohol/d. There was significant ($P = 0.01$) heterogeneity between studies in the stratum of nonsmokers by sex but not among the current and former smokers (data not shown). In male never smokers, the risk of lung cancer was greater in the consumption category of ≥15 g alcohol/d than in the category of no alcohol consumption (pooled multivariate RR: 6.38; 95% CI: 2.74, 14.9; *P* for trend < 0.001). In the same comparison in the women, the increase was more

TABLE 5
Alcohol consumption and lung cancer by smoking status: pooled multivariate-adjusted relative risks (RR)

	Alcohol consumption (g/d)				*P* for trend	*P* for between-studies heterogeneity for ≥15 g alcohol/d category	*P* for between-studies heterogeneity due to smoking status for ≥15 g alcohol/d category
	None	>0 to <5	5 to <15	≥15			
Men							
Nonsmokers[1]							
No. of cases	10	16	18	30	<0.001	0.51	
RR	1.0[2]	1.49	2.53	6.38			
95% CI	—	0.64, 3.49	1.10, 5.81	2.74, 14.90			
Former smokers[1]							
No. of cases	99	139	161	236	0.27	0.91	
RR	1.0[2,3]	0.72	0.87	0.94			
95% CI	—	0.54, 0.98	0.65, 1.17	0.71, 1.25			
Current smokers							
No. of cases	145	218	253	437	0.92	0.22	<0.001
RR	1.0[2,4]	0.85	1.01	0.94			
95% CI	—	0.52, 1.38	0.75, 1.37	0.72, 1.24			
Current smokers (<20 cigarettes/d)							
No. of cases	67	93	105	121	0.12	0.81	
RR	1.0[2,4]	0.83	1.01	0.76			
95% CI	—	0.42, 1.66	0.69, 1.47	0.53, 1.11			
Women							
Nonsmokers							
No. of cases	90	68	17	8	0.98	0.52	
RR	1.0[2]	0.98	0.89[5]	1.35[5,6]			
95% CI	—	0.69, 1.37	0.52, 1.54	0.64, 2.87			
Former smokers							
No. of cases	112	82	72	72	0.26	0.19	
RR	1.0[2,3]	0.68	0.85	1.11			
95% CI	—	0.39, 1.16	0.59, 1.21	0.69, 1.79			
Current smokers							
No. of cases	265	194	163	232	0.02	0.62	0.76
RR	1.0[2,4]	0.76	0.85	1.10			
95% CI	—	0.59, 0.97	0.69, 1.05	0.90, 1.33			
Current smokers (<20 cigarettes/d)							
No. of cases	102	62	60	62	0.42	0.50	
RR	1.0[2,4]	0.61	0.79	0.94			
95% CI	—	0.43, 0.87	0.55, 1.12	0.66, 1.33			

[1] Does not include the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study, which was limited to current smokers.

[2] Adjusted for education (<high school graduate, high school graduate, or >high school graduate), BMI (<23, 23 to <25, 25 to <30, or ≥30; in kg/m^2), and energy intake (continuous).

[3] Also adjusted for smoking duration (continuous).

[4] Also adjusted for smoking duration (continuous) and cigarettes smoked daily (continuous).

[5] The Canadian National Breast Screening Study did not have any female nonsmokers in the 5 to <15 g alcohol/d and ≥ 15 g alcohol/d categories and was not included in these categories but was included in the 2 lower categories.

[6] The New York State Cohort did not have any female nonsmokers in the ≥15 g alcohol/d category and was not included in this category but was included in the 3 lower categories.

modest and the CI included the null (pooled multivariate RR: 1.35; 95% CI: 0.64, 2.87; *P* for trend = 0.98), but the estimate was based on only 8 cases in the highest category, and 2 of the cohorts had no cases in that category. In both male and female former smokers, alcohol consumption was not associated with risk of lung cancer.

We also examined risk associated with alcohol consumption in former smokers who had quit smoking ≥10 y before the baseline. There was no association between alcohol consumption and risk in this group (data not shown). For current smokers, upper-category pooled multivariate RRs were 0.94 and 1.10 for men and women, respectively, and CIs included the null (*P* for trend were = 0.92 and 0.02, respectively). When we examined the association between alcohol consumption and lung cancer risk in current smokers who reported smoking <20 cigarettes/d at baseline, we found no association. The association between alcohol consumption and lung cancer risk was modified by smoking status in men but not in women ($P < 0.001$ and = 0.76, respectively, for between-studies heterogeneity by smoking status in the upper category of alcohol consumption). We also examined beverage-specific analyses stratified by smoking status; the number of cases in each category was small, and the CIs were wide. Whereas there was evidence of an inverse association with wine consumption in men in the overall group, when results were

TABLE 6
Alcohol consumption (g/d) and lung cancer by histologic type: pooled multivariate-adjusted relative risks (RR)[1]

	Alcohol consumption (g/d)					*P* for trend	*P* for between-studies heterogeneity for ≥30 g alcohol/d category	*P* for common effect by cell type for ≥30 g alcohol/d category
	None	>0 to <5	5 to <15	15 to <30	≥30			
Men								
Adenocarcinoma								
No. of cases	54	82	104	53	80	0.10	0.33	
RR	1.0	1.06	1.24	1.00	1.44			
95% CI	—	0.79, 1.41	0.94, 1.62	0.69, 1.46	1.01, 2.06			
Squamous cell								
No. of cases	92	132	158	131	140	0.64	<0.01	
RR	1.0	0.91	0.98	0.81	1.05			
95% CI	—	0.70, 1.18	0.75, 1.29	0.55, 1.19	0.52, 2.12			
Small cell								
No. of cases	34	59	58	68	61	<0.01	0.48	0.51
RR	1.0	1.10	1.15	1.08	1.65			
95% CI	—	0.80, 1.50	0.85, 1.56	0.79, 1.47	1.19, 2.29			
Women								
Adenocarcinoma								
No. of cases	178	151	115	55	81	<0.01	0.20	
RR	1.0	0.92	0.92	0.96	1.40			
95% CI	—	0.75, 1.13	0.73, 1.15	0.72, 1.30	0.98, 1.98			
Squamous cell								
No. of cases	86	58	45	21	31	0.99	0.15	
RR	1.0	0.72	0.76	0.80	0.92[2]			
95% CI	—	0.49, 1.06	0.57, 1.03	0.55, 1.18	0.55, 1.54			
Small cell								
No. of cases	90	58	50	28	30	0.94	0.79	0.26
RR	1.0	0.81	0.77	0.99	0.89			
95% CI	—	0.61, 1.05	0.56, 1.06	0.63, 1.54	0.62, 1.29			

[1] Adjusted for education (<high school graduate, high school graduate, or >high school graduate), BMI (<23, 23 to <25, 25 to <30, or ≥30; in kg/m^2), energy intake (continuous), smoking status (never, past, or current), smoking duration for past and current smokers (continuous), and cigarettes smoked daily for current smokers (continuous).

[2] The New York State Cohort did not have any cases of squamous cell carcinomas among females in the ≥30 g alcohol/d category and was not included in this category but was included in the 4 lower categories.

stratified by smoking status, this inverse association was observed only in former smokers (pooled multivariate RR: 0.54; 95% CI: 0.29, 1.01 for ≥15 versus 0 g alcohol/d); for never and current smokers, there was a nonsignificantly greater risk in association with wine drinking (data not shown).

We examined risk by tumor histology (**Table 6**). In the highest category of alcohol consumption, there was significant between-studies heterogeneity by sex for small-cell carcinomas ($P = 0.01$) but not for adenocarcinomas and squamous cell carcinomas (data not shown). There was some evidence that alcohol consumption was more strongly associated with the risk of adenocarcinomas in both men and women and with the risk of small-cell tumors in men. However, the difference in the RRs was not significant; for men and women in the ≥30 g alcohol/d category, *P* for common effects according to cell type was 0.51 and 0.26, respectively.

Residual confounding by smoking was a concern in our analyses. We therefore examined the effect on results if all participants coded as never smokers were in fact former smokers. We recalculated RRs after assigning all never smokers the study-specific median duration of smoking reported by former smokers. These RRs were quite similar to our original calculations; CIs overlapped almost completely (data not shown). Because there might be more misclassification in reported smoking status in the heavier drinkers, we also examined a model in which we reclassified as former smokers the never smokers in the upper category of alcohol drinking. For this latter analysis, the RRs were closer to the null than in the original analyses, and the CIs included the null. Nonetheless, the *P* for trend was 0.05 for the men (data not shown).

We also examined whether there were differences in risk associated with alcohol consumption for dichotomous strata of fruit, β-cryptoxanthin, folate and vitamin A consumption determined by their respective median values. There was no evidence of heterogeneity in effects across strata (data not shown).

DISCUSSION

In this pooled analysis, there was weak evidence for a positive association between alcohol consumption and lung cancer risk. Trends were significant, although the CIs for the risk estimates in the highest category of alcohol consumption included the null. In men, the consumption of spirits was associated with risk more than was that of other beverage types; in women, risk was associated with the consumption of beer than with that of wine or spirits. There was a strong positive association between alcohol consumption and risk in never smoking men that was not observed in female never smokers. However, the small number of

female cases who were never smokers in the highest drinking category limited our ability to examine associations in this group. There was no evidence of an association of alcohol consumption with risk in smokers, who constitute the largest portion of cases in these cohorts.

Several potential mechanisms have been proposed for an effect of alcohol on lung cancer. These include carcinogenesis by the alcohol metabolite acetaldehyde (3), oxidation by alcohol (4–12), and induction by alcohol of cytochrome p450 that affects the metabolism of other procarcinogens (4, 13). Other compounds in alcoholic beverages may also be relevant (2), which could explain the different associations we saw for beer and spirits than for wine. However, we saw differences in beverage-specific associations in both men and women; the observed beverage-specific differences may not be biological. Furthermore, it has been hypothesized that the mechanism of alcohol may be to enhance carcinogenic effects of cigarette smoke on tissues (2); our findings were strongest for nonsmokers, however, which would not be consistent with this explanation.

Many epidemiologic studies have examined the association between alcohol consumption and lung cancer, and the results have been inconsistent (2), perhaps as a result of the strong effect of smoking on lung cancer risk, the likely weak effect (if any) of alcohol, and the different sizes of the studies. In a meta-analysis of studies of alcohol consumption and lung cancer (22), point estimates for combined findings in 13 cohorts [including 2 of the cohorts in our pooled analyses (31, 48)] were similar to those we report here. These investigators also conducted a meta-analysis of 10 case-control studies; there was an increase in lung cancer risk associated with alcohol consumption in hospital-based but not population-based case-control studies (22). In 2 cohort studies not included in our analysis (49, 50) and in several case-control studies (51–53) published since the publication of the meta-analysis, findings were also consistent with ours.

Because smoking is such a strong risk factor for lung cancer and because smoking is correlated with alcohol consumption, the major concern in the examination of an association between alcohol consumption and lung cancer is failure to fully control for confounding by smoking. Measurement error in measured aspects of smoking (ie, smoking status, duration of smoking, and amount smoked) and variations in other unmeasured aspects (ie, depth of inhalation and length of time that smoke is held in the lungs) may have an effect on the estimation of the risk of lung cancer from other factors correlated with smoking, such as alcohol (2, 22, 54). It may be that our findings of differences by beverage type may be the result of uncontrolled confounding. Of interest with respect to residual confounding by smoking is our finding of a large increase in risk of lung cancer in men who never smoked. There have been several other studies of alcohol consumption and lung cancer in nonsmokers (22, 55–58). Most of these studies have found an increased risk associated with alcohol consumption, albeit generally at somewhat lower levels of alcohol consumption.

By contrast with the findings of increased risk in male never smokers, we found little evidence of increased risk in former and current smokers in our study, even in those who had quit smoking $\geq$10 y before or for current smokers of $<$20 cigarettes/d, groups that should be more similar to the never smokers with respect to their lung cancer risk. There was some evidence that female current smokers in the highest category of alcohol consumption were at increased risk. Whereas the CI for the highest category included the null, there was evidence of a significant trend in the data. Other studies have reported increased risk with alcohol consumption in heavy smokers (2, 59, 60).

Because of our finding of increased risk of lung cancer with alcohol consumption in men who reported never smoking, we investigated the possible effect of a misreporting of smoking status on the estimate of risk by recalculating risk estimates after reclassifying never smokers as former smokers. Risk estimates changed only somewhat. In contrast, in simulations regarding misclassification by smoking status, Korte et al (22) found that the RR for their meta-analysis of cohort studies was consistent with no true effect, 10% misclassification of smokers as nonsmokers, and no misclassification of drinking status.

An additional potential source of residual confounding could be the effect of passive smoke exposure. In particular, the group of nonsmokers who were included in the highest category of alcohol consumption might have a heavier exposure to smoke if they drank in smoke-filled environments. We had limited or no information on passive smoke exposure in all but one of the cohorts. However, passive smoke exposure is unlikely to explain an association of the magnitude of that observed in nonsmoking men. Furthermore, there may be some confounding due to the smoking of pipes and cigars. Limited information was available on the smoking of pipes and cigars in the current study.

Misclassification of drinking status—particularly the inclusion of former drinkers in those reporting that they are currently nondrinkers—is another potential source of bias. Misclassification of this nature would attenuate risk estimates if alcohol consumption does increase lung cancer risk. In fact, there was some indication in both men and women that there was a lower risk of cancer in those reporting moderate consumption than in nondrinkers. Our findings were also consistent with an alcohol effect limited to heavier drinking. Because of smaller numbers of heavier drinkers, we were not able to explore in detail the associations with heavy alcohol consumption.

We found some evidence of differences in the association between different beverage types and the risk of lung cancer: a stronger association for spirits in men and for beer in women. Other studies have found greater risk in association with consumption of beer and spirits but not wine (2). These differences may be related to compounds found in beer or spirits. When we looked at more closely defined categories of the consumption of spirits by the men, the increased risk was again primarily confined to those drinking $\geq$30 g alcohol/d.

In this study, which entailed pooling data from the cohorts of 7 studies with a total sample of nearly 400 000 participants and $>$3000 lung cancer cases, we found weak evidence of a positive association between alcohol consumption and lung cancer risk. By pooling data from these large cohort studies, we were able to examine risk in uniformly defined exposure groups and with a consistent group of covariates. The observed risk appeared to be confined to those subjects with consumption of $\geq$30 g alcohol/d, which corresponds to $\geq$2 drinks/d. However, we could not exclude the possibility, at least in the smokers, that this association could be explained by uncontrolled confounding by smoking. The finding of an increased RR in male never smokers is notable, although the absolute risk of lung cancer in this group is, of course, small. Smoking remains the most important cause of this disease, which has considerable effect on public health.

Pooled data came from existing cohorts. Investigators for each study had contributed to the design of and data collection and analysis of their particular study.

When these analyses were initiated, DJH was the principal investigator for the Pooling Project, leading the overall effort to conduct data analysis on existing data sets. SAS-W (the current principal investigator for the Pooling Project) worked with JLF, DJH, and JR on management of the data and in all phases of data analysis and manuscript writing. The data analysis plan was conceived by JLF. Data analyses were conducted by JR. All other authors contributed to the data analysis plan. The manuscript was written by JLF with input from all of the other authors. None of the authors had a personal or financial conflict of interest.

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